## REMARKS

Applicants respectfully request entry of amendments to claim 1. Support for the amendments can be found throughout the specification, including paragraph [0173], Examples 1 through 5, and Figures 4-7, 9, and 12-16, and the originally filed claims and, therefore, do not add new matter.

Applicants submit that pending claims 1 and 83-115 are in condition for allowance, and respectfully request that the claims as amended be entered.

**Rejections Under 35 U.S.C. §112, Second Paragraph**

Claims 1 and 83-115 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Claim 1 is alleged to be indefinite for the recitation of the phrase "gene encoding region." Applicants submit that this allegation is incorrect. A "gene encoding region" is an art recognized term that means a nucleic acid sequence which produces a product.[1] In cells, genes consist of a long strand of DNA that contains a promoter, which controls the activity of a gene, and coding and non-coding sequences. The coding sequence determines what the gene produces, while non-coding sequences can regulate the conditions of gene expression. Therefore, a gene encoding region cannot consist of a promoter region or an intron.

Accordingly, Applicants respectfully submit that the claims are not indefinite because one skilled in the art, at the time the application was filed, would understand the metes and bounds of the subject matter of Applicant's invention. Withdraw of the rejection is respectfully requested.

---

[1] *See, e.g.*, <http://en.wikipedia.org/wiki/Gene>, last visited July 22, 2008.

**Rejection Under 35 U.S.C. §101**

Claims 1 and 83-115 are rejected under 35 U.S.C. §101, allegedly because the disclosed invention is inoperative and lacks utility. Applicants respectfully traverse the rejection as it applies to the pending amended claims.

The Office Action alleges that the claimed method does recite a physical transformation of matter (i.e. contacting samples with a SNPs). However, the Office Action also alleges that the claimed invention as a whole results in "identifying" a population structure, which is not a tangible result.

Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 1 to recite a method of inferring, with a predetermined level of confidence, proportional ancestry of at least two ancestral groups of a test individual by identification of a population structure comprising the steps of: a) determining single nucleotide polymorphisms (SNPs) for a first population and identifying a first population of SNPs having a frequency differential ($\delta$) > 0.4 between one or more pairs of population groups; b) contacting a parental sample nucleic acid with one or more hybridizing nucleic acids corresponding the first population of SNPs, wherein the one or more hybridizing nucleic acids selectively hybridize to the nucleic acid in the parental sample; c) selecting SNPs hybridizing in step (b) to generate a second population of SNPs which have a minor allele frequency > 1% and a $\delta$ > 0.4 for at least one pair of the at least two population groups, wherein at least one of the second population of SNPs is a SNP which may be correlated with but not linked to a gene-linked trait, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region; d) contacting a sample comprising nucleic acid molecules of a test individual with the second population of SNPs, wherein the second population of SNPs are indicative of a population structure, and wherein the population structure is correlated with a trait of the test individual; e) determining the nucleotide occurrences of the second population of SNPs in the sample from the test individual; and f) identifying the population structure indicated by the nucleotide occurrences determined for the test individual, wherein identifying the population structure infers the proportional ancestry of

the test individual; and g) providing information resulting from steps (a) through (f) to a user. step of providing information resulting from steps (a) through (f) to a user. Support for this amendment can be found in, for example, paragraph [0173], Examples 1 through 5, and Figures 4-7, 9, and 12-16 in the specification as filed.

In light of these amendments, Applicants respectfully submit that the claims produce a tangible result, and request withdrawal of the rejection.

**Rejections Under 35 U.S.C. §103**

As an initial matter, in response to Applicant's arguments filed on 1/11/2008, the Office Action stated that "applicant's arguments that the cited prior art does not teach SNPs at 'neutral loci' are not persuasive since the claims do not recite 'neutral loci.' This limitation is interpreted as SNPs in non-encoding regions. It is also noted that the specification does not provide a limiting definition for 'gene encoding region.'" (Office Action, page 11.) As detailed above, a "gene encoding region" is an art recognized term that means a nucleic acid sequence which produces a product. Thus, a population of SNPs "not located within a gene encoding region" would necessarily include non-coding sequences such as introns, promoter, and 3' gene sequences.

Claims 1, 83-86, 90-101 and 104-109 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Parra et al., in view of Shriver et al, in view of Kaessmann et al., and in view of Vines. Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The standard that has to be satisfied in order to make a valid rejection based on a *prima facie* case of obviousness has been modified recently by the recent Supreme Court decision in *KSR International v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ 2d. 1385 (2007). Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or

combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references. The Applicants respectfully submit that the Office Action has not established a *prima facie* case of obviousness.

The Office Action alleges that Parra "teaches a method for inferring ancestral proportions and admixture in six different populations from different regions." (Office Action, page 6.) The Office Action also alleges, in pertinent part, that "Parra does not specifically teach selecting SNPs to generate a second population of SNPs that are not located within a gene encoding region, as in claim 1." (Office Action, page 7.) The Office Action then alleges that "Shriver teaches a method for identifying a set of genetic markers using likelihood analysis that allows the confident determination of ethnicity for use in a forensic setting. In particular, Shriver presents population specific alleles." (Office Action, page 8.) The Office Action also provides Kaessmann, which allegedly "teaches the use of non-coding region DNA for purposes of determining point mutations and gaining insight to human ancestry." (Office Action, page 8.) Lastly, the Office Action provides Vines to "show the benefit of using 'neutral' loci and junk DNA for determining ancestry in genomic ancestry applications and forensic science applications." (Office Action, page 8.)

The Office Action stated that it would have been "obvious to one of ordinary skill in the art to modify the method of Parra to select a second set of SNPs from non-coding region mutations as taught by Shriver and Kaessmann, since DNA markers offer little power to distinguish ethnicity of an individual, as suggested by Shriver. One of ordinary skill in the art would have been motivated to combine the above teachings in order to improver ancestral prediction by using markers from non-coding DNA regions that are highly unlikely to be the direct target of positive or negative selection, as suggested by Kaessmann with predictable results, as suggested by Vines." (Office Action, page 8.) Applicants respectfully disagree.

The claims as currently amended are drawn to a method of inferring, with a predetermined level of confidence, proportional ancestry of at least two ancestral groups of a test individual by identification of a population structure comprising the steps of: a) determining

single nucleotide polymorphisms (SNPs) for a first population and identifying a first population of SNPs having a frequency differential ($\delta$) > 0.4 between one or more pairs of population groups; b) contacting a parental sample nucleic acid with one or more hybridizing nucleic acids corresponding the first population of SNPs, wherein the one or more hybridizing nucleic acids selectively hybridize to the nucleic acid in the parental sample; c) selecting SNPs hybridizing in step (b) to generate a second population of SNPs which have a minor allele frequency > 1% and a $\delta$ > 0.4 for at least one pair of the at least two population groups, wherein at least one of the second population of SNPs is a SNP which may be correlated with but not linked to a gene-linked trait, wherein the second population of SNPs is an autosomal SNP, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region; d) contacting a sample comprising nucleic acid molecules of a test individual with the second population of SNPs, wherein the second population of SNPs are indicative of a population structure, and wherein the population structure is correlated with a trait of the test individual; e) determining the nucleotide occurrences of the second population of SNPs in the sample from the test individual; f) identifying the population structure indicated by the nucleotide occurrences determined for the test individual, wherein identifying the population structure infers the proportional ancestry of the test individual; and g) providing information resulting from steps (a) through (f) to a user.

Perra et al described the use of linked autosomal markers, mtDNA, and Y-chromosome markers located in gene coding regions in the study of ancestral proportions and admixture dynamics (See, e.g., Abstract; page 19, Col. 2 to page 20, Col. 1). Perra does not describe a second population of SNPs as in claim 1, step c), where the SNP may be correlated with but not linked to a gene-linked trait, wherein the second population of SNPs is an autosomal SNP, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region. The markers used in Parra et al. include, for example, apolipoprotein A (APO A), AT3, antithrombin 3 (AT3), DUFFY antigen (FY), tyrosinase mutation (OCA2) and vitamin D binding protein (GC), and are all located within a gene encoding region.

The deficiency in Perra is not cured by the secondary references. The Office Action alleges that "Shriver teaches a method for identifying a set of genetic markers using likelihood analysis that allows the confident determination of ethnicity for use in a forensic setting. In particular, Shriver presents population specific alleles." (Office Action, page 8.) Shriver describes the use of markers within gene coding regions to estimate ethnic-affiliation. Again, the method as claimed requires that at least one SNP correlate with but not linked to a gene-linked trait, wherein the second population of SNPs is an autosomal SNP, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region.

The Office Action also provides Kaessmann, which allegedly "teaches the use of non-coding region DNA for purposes of determining point mutations and gaining insight to human ancestry." (Office Action, page 8.) A review of Kaessmann indicates that phylogenetic trees were constructed based on DNA sequence strings from the X chromosome, which is a non-autosomal DNA.[2] Claim 1 requires that at least one SNP correlate with but not linked to a gene-linked trait, wherein the second population of SNPs is an autosomal SNP, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region. Lastly, the Office Action provides Vines to "show the benefit of using 'neutral' loci and junk DNA for determining ancestry in genomic ancestry applications and forensic science applications." (Office Action, page 8.) There is nothing in the cited reference which discloses or suggests the required elements of the current independent claim i.e., a method of inferring, with a predetermined level of confidence, proportional ancestry of at least two ancestral groups of a test individual by identification of a population structure comprising the steps of: a) determining single nucleotide polymorphisms (SNPs) for a first population and identifying a first population of SNPs having a frequency differential ($\delta$) > 0.4 between one or more pairs of population

---

[2] See, e.g., the definition of an autosome from Wikipedia: "An autosome is a non-sex chromosome. It is an ordinarily paired type of chromosome that is the same in both sexes of a species. For example, in humans, there are 22 pairs of autosomes. The X and Y chromosomes are not autosomal. Non-autosomal chromosomes are usually referred to as sex chromosomes, allosomes or heterosomes." <http://en.wikipedia.org/wiki/Autosomal>, last visited July 23, 2008.

groups; b) contacting a parental sample nucleic acid with one or more hybridizing nucleic acids corresponding the first population of SNPs, wherein the one or more hybridizing nucleic acids selectively hybridize to the nucleic acid in the parental sample; c) selecting SNPs hybridizing in step (b) to generate a second population of SNPs which have a minor allele frequency > 1% and a $\delta > 0.4$ for at least one pair of the at least two population groups, wherein at least one of the second population of SNPs is a SNP which may be correlated with but not linked to a gene-linked trait, wherein the second population of SNPs is an autosomal SNP, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region; d) contacting a sample comprising nucleic acid molecules of a test individual with the second population of SNPs, wherein the second population of SNPs are indicative of a population structure, and wherein the population structure is correlated with a trait of the test individual; e) determining the nucleotide occurrences of the second population of SNPs in the sample from the test individual; f) identifying the population structure indicated by the nucleotide occurrences determined for the test individual, wherein identifying the population structure infers the proportional ancestry of the test individual; and g) providing information resulting from steps (a) through (f) to a user.

Applicants submit that because the cited references do not teach all the claim limitations, one of skill in the art would not be motivated to combine the reference teachings. In addition, the Office Action has not shown that the combination of references suggests a reasonable expectation of success of performing the method as claimed, nor do the prior art references teach or suggest all of the recited claim limitations, thus no *prima facie* case for obviousness exists. Accordingly, withdrawal of rejection under 35 U.S.C. §103 is respectfully requested.

Claims 87-89 and 110-115 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Parra et al., in view of Shriver et al, in view of Kaessmann et al., in view of Vines, and further in view of Sorenson et al.. Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicants submit that because the cited references do not teach all the claim limitations, one of skill in the art would not be motivated to combine the reference teachings.

The Office Action alleges, in pertinent part, that Parra, Shriver, Kaessmann and Vines do not specifically teach contacting samples with high numbers of SNPs as in claims 87-89, nor do the references teach proportional ancestries comprising a photo of a person from whom the known proportional ancestry was determined, as in claims 110-115. (Office Action, page 9.) The Action the provides Sorenson et al., which is alleged to teach a genealogical research and record keeping system for identifying commonalities in haplotypes from biological samples. The Office Action alleges that it "would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method made obvious by Parra, Shriver, Kaessmann, and Vines using high numbers of SNPs and image data as taught by Sorenson et al., in order to identify previously unknown biological relationships by automatically correlating genetic information with genealogical information, resulting in the practice of the instantly claimed invention with predictable results." (Office Action, page 9.)

The deficiencies identified in the combination of Parra et al., in view of Shriver et al, in view of Kaessmann et al., and in view of Vines have been covered above, and will not be reiterated here. All the limitations of claim 1, from which claims 87-89 and 110-115 depend, are not taught by Sorenson. Sorenson does not describe a method of inferring proportional ancestry using second population of SNPs as in claim 1, step c), where the SNP may be correlated with but not linked to a gene-linked trait, wherein the second population of SNPs is an autosomal SNP, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region.

Applicant's claims do not refer to genealogical research and record keeping system for identifying commonalities in haplotypes from biological samples, as the Office Action alleges Sorenson describes, but rather identification of population structure demonstrating proportional ancestry, which is determined using autosomal, non-coding markers. Sorenson describes a database matching method for determining hierarchical trees, otherwise known as family trees, which is an extended form of paternity analysis, which relies on the concept of identity by

descent, by assigning individuals to groups based on commonality of haplotype sequences. (See, e.g. Claims 1-52, paragraph [0031-0033].) There are no examples in Sorenson of autosomal, non-coding SNPs that are informative for proportional ancestry, as in the present claims.

Additionally, the term "genetic characteristics" in Sorenson refers to phenotypes, not mutations or polymorphisms. (See, e.g., paragraph [0009].) Sorenson focuses on haplotypes, which are matched among individuals and extended pedigrees to determine to which the individual belongs. The abstract states "A genealogical research and record keeping system and method for identifying commonalities in haplotypes and other genetic characteristics of two or more individual members of a biological sample." The claim for a method for (directly) "identifying commonalities in genetic characteristics correlated with specific genetic markers" [0002], specifically using haplotypes constructed of repeats or SNPs, is distinct from Applicant's claims which contain a method of inferring proportional ancestry using second population of SNPs as in claim 1, step c), where the SNP may be correlated with but not linked to a gene-linked trait, wherein the second population of SNPs is an autosomal SNP, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region.

Applicants submit that, in fact, the cited references "teach away" from the present invention. One of skill in the art would only extract from such teachings confounded relationships due the exclusive use of haplotypes strictly coupled to phenotype. As such, the references do not teach the purpose of determining ancestry by using SNPs that are not linked to a gene-linked trait, and thus, the purpose of Applicants' invention could not be accomplished using the teachings of the cited references. Therefore, the references teach away, since the impression left to the skilled artisan is that the method would not have the property sought by Applicants. *In re Caldwell*, 319 F.2d 254, 256, 138 USPQ 243, 245 (CCPA 1963).

Because the teachings of Parra et al. would not result in a method for determining ancestry as claimed when combined with the teachings of Shriver, Kaessmann, Vines, or Sorenson, one of skill in the art would not have an expectation of success because the invention as claimed would not be achieved in view of such teachings. Thus, since the limitations of independent claim 1 are not met, it is irrelevant whether Sorenson teaches contacting samples

with high numbers of SNPs as in dependent claims 87-89; it is also irrelevant whether Sorenson teaches proportional ancestries comprising a photo of a person from whom the known proportional ancestry was determined, as in dependent claims 110-115. Therefore, one of skill in the art would not be motivated to combine such teachings.

Applicants submit that because there is no reasonable expectation of successfully achieving the invention as claimed, there is no motivation to combine the cited references, thus, no *prima facie* case for obviousness exists. For these reasons, Applicants respectfully request that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claims 102 and 103 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Parra et al., in view of Shriver et al, in view of Kaessmann et al., in view of Vines, and further in view of Pritchard et al.. Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicants submit that because the cited references do not teach all the claim limitations, one of skill in the art would not be motivated to combine the reference teachings.

The Office Action alleges, in pertinent part, that Parra, Shriver, Kaessmann and Vines do not specifically teach generating a graphical representation as in claims 102 and 103. (Office Action, page 10.) The Action the provides Pritchard et al., which is alleged to teach methods for inferring proportional ancestry of different ancestral groups, and graphically displaying ancestral results in triangular format, and also teaches a computer-based program STRUCTURE for estimating population struction fur 20 data sets of 50, 200, and 1000 biallelic markers. genealogical research and record keeping system for identifying commonalities in haplotypes from biological samples. The Office Action alleges that it "would have been obvious to one of ordinary skill in the art at the time of the instant invention to practice the method made obvious by Parra, Shriver, Kaessmann, and Vines with an additional step for generating ancestral maps and displaying results in triangular format, as taught by Pritchard, since both Parra and Shriver present their results in graphical format, as set forth above, and since Pritchard also estimates population structure." (Office Action, page 10.)

The deficiencies identified in the combination of Parra et al., in view of Shriver et al, in view of Kaessmann et al., and in view of Vines have been covered above, and will not be reiterated here. All the limitations of claim 1, from which claims 102 and 103 depend, are not taught by Pritchard. Pritchard does not describe a method of inferring proportional ancestry using second population of SNPs as in claim 1, step c), where the SNP may be correlated with but not linked to a gene-linked trait, wherein the second population of SNPs is an autosomal SNP, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region.

Applicant's claims do not refer to generating ancestral maps and displaying results in triangular format, as the Office Action alleges Pritchard describes, but rather identification of population structure demonstrating proportional ancestry, which is determined using autosomal, non-coding markers. There are no examples in Pritchard of autosomal, non-coding SNPs that are informative for proportional ancestry, as required by the present claims.

Additionally, Pritchard focuses on haplotypes and phenotypes, which are matched among individuals and extended pedigrees to determine to which the individual belongs. (See, e.g., page 228, Col. 2 and page 229, Col. 1.) Applicant's claims contain a method of inferring proportional ancestry using second population of SNPs as in claim 1, step c), where the SNP may be correlated with but not linked to a gene-linked trait, wherein the second population of SNPs is an autosomal SNP, and wherein the at least one SNP of the second population of SNPs is not located within a gene encoding region.

Because the teachings of Parra et al. would not result in a method for determining ancestry as claimed when combined with the teachings of Shriver, Kaessmann, Vines, or Pritchard, one of skill in the art would not have an expectation of success because the invention as claimed would not be achieved in view of such teachings. Thus, since the limitations of independent claim 1 are not met, it is irrelevant whether Pritchard teaches generating ancestral maps and displaying results in triangular format as in dependent claims 102 and 103. Therefore, one of skill in the art would not be motivated to combine such teachings.

Applicants submit that because there is no reasonable expectation of successfully achieving the invention as claimed, there is no motivation to combine the cited references, thus, no *prima facie* case for obviousness exists. For these reasons, Applicants respectfully request that the rejection, including as it might be applied against the amended claims, be withdrawn.

**Conclusion**

Applicants submit that pending claims 1 and 83-115 are in condition for allowance. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

The Commissioner is hereby authorized to charge the total amount of $60.00 to Deposit Account No. 07-1896 as payment for the One-Month Extension of Time fee. No additional fee is believed due in connection with this Response. However, the Commissioner is further authorized to charge any additional fees required by this submission, or make any credits or overpayments, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: August 19, 2008

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA Piper US LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
**USPTO Customer Number 28213**